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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,519	03/05/2002	Guido Krupp	P-UX 4977	9641
41552	7590	03/11/2005		
MCDERMOTT, WILL & EMERY 4370 LA JOLLA VILLAGE DRIVE, SUITE 700 SAN DIEGO, CA 92122			EXAMINER STRZELECKA, TERESA E	
			ART UNIT 1637	PAPER NUMBER
DATE MAILED: 03/11/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/937,519

Applicant(s)

KRUPP, GUIDO

Examiner

Teresa E Strzelecka

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 2,4 and 12-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3 and 5 is/are rejected.
- 7) ☒ Claim(s) 1,3, 5-11 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/22/2002.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Notice to Comply.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1, 3 and 5-11) in the reply filed on December 22, 2004 is acknowledged. The traversal is on the ground(s) that search for the method of Group I will likely reveal information relevant to the examination of Group II. This is not found persuasive because, as Applicant states in the last paragraph of page 10 of the response, the claims of Groups I and II are patentably distinct. Further, they are patentably distinct because claims of Group I are drawn to real-time detection of any nucleic acid with a primer comprising a 5'-GAAA-3' sequence motif and detection probe comprising a 5'-CUGANGA-3' sequence motif, whereas the claims of Group II are drawn to real-time detection of any nucleic acid with a primer comprising 5'-CUGANGA-3' motif and detection probe comprising a 5'-GAAA-3' sequence motif. Therefore, search for the method of Group I would not necessarily reveal a reference applicable as prior art for the method of Group II.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2, 4 and 12-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 22, 2004.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on January 22, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Sequence Rules Compliance

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN time of reply to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

The following pages contain sequences which do not have SEQ ID NOs: page 16-18 (Table I), page 19-23 (Table II), page 28 and pages 30-32.

Claim Objections

5. Claims 1, 3 and 5-11 are objected to because of the following informalities: claims do not have active method steps. For example, in claim 1, step a) should read "using a primer" instead of "primer is used", in step b), "carrying out the amplification" rather than "amplification being carried out", etc. Appropriate correction is required.

6. Claims 6-11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite over the recitation of “a primer is used to which a nucleic acid sequence, preferably with a length of 1 to 40 nucleotides, is attached” (step a). It is not clear whether the phrase “preferably with a length of 1 to 40 nucleotides” is meant to be a limitation of the claim, therefore, it is not clear what are the metes and bounds of the claim.

B) Claim 1 is indefinite over the recitation of “the amplification being carried out in the presence of an excess, preferably in a concentration of 50 to 500 nM, of a nucleic acid probe, preferably with a length of 25 to 60 nucleotides (particularly preferably approx. 50 nucleotides)” (step b). It is not clear whether the phrases “preferably in a concentration of 50 to 500 nM” and “preferably with a length of 25 to 60 nucleotides (particularly preferably approx. 50 nucleotides)” are meant to be claim limitations, therefore, it is not clear what are the metes and bounds of the claim.

C) Claim 1 is indefinite over the recitation of “the relative concentration” in step c). Step c) is drawn to determining the original concentration of the nucleic acid in the sample and no relationship has been provided between the original concentration and the relative concentration.

D) Claim 3 is indefinite over the recitation of “the sequence range of the nucleic acid which contains motif A” (step a). It is not clear what this term means.

E) Claim 3 is indefinite over the recitation of “the relative concentration” in step c). Step c) is drawn to determining the original concentration of the nucleic acid in the sample and no relationship has been provided between the original concentration and the relative concentration.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1, 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uijtewaal et al. (EPO 0 416 572 A1), Leone et al. (Nucl. Acids Res., vol. 26, pp. 2150-2155, 1998) and Heid et al. (Genome Research, vol. 6, p. 986-994, 1996).

A) Regarding claims 1 and 3, Uijtewaal et al. teach construction of ribozyme-encoding oligonucleotides with sequences complementary to sequences of plant proteins, such as polygalacturonase, pectin esterase and ripening related protein. The ribozymes contained sequence motifs 5'-GAAA-3' and 5'-CTGATGA-3', which, after expression in plants, produced a motif of 5'-CUGAUGA-3' (page 3, lines 28-58; page 4, lines 47-58; page 5, lines 1-16; page 8, lines 1-44).

Uijtewaal et al. teach transformation of ribozyme-encoding vectors into tomato plants and detection of the ribozyme sequences by hybridization of the oligonucleotides containing the 5'-CTGATGA-3' motif with total RNA isolated from transgenic plants (page 6, lines 18-58; page 7, lines 1-29).

Regarding claim 5, Uijtewaal et al. teach RNA (page 8, lines 23-44).

B) Uijtewaal et al. do not teach real-time detection of the ribozymes using a probe labeled with a reporter and a quencher.

C) Regarding claims 1 and 3, Leone et al. teach detection of RNA of potato leaf roll virus (PLRV) in potato tubers using real-time NASBBA amplification reaction with a probe containing a reporter molecule and a quencher molecule (Abstract; page 2151, paragraphs 3-5 and 10; page 2152, first paragraph). Leone et al. teach determination of the different amounts of the PLRV in the samples using real-time NASBA (page 2153, last two paragraphs; page 2154, first and second paragraph; Fig. 3 and 7).

D) Leone et al. do not teach determination of the original concentration of nucleic acids using the threshold values for the sample and reference.

E) Heid et al. teach real time quantitative PCR (Abstract), in which the threshold value C_T , equal to a number of amplification cycles, and, therefore, time, after which the fluorescence becomes detectable, is related to the number of nucleic acid molecules in the reaction (Fig. 1; page 988; page 989, first paragraph). The relationship between C_T values and the amount of input target sequences is quantitative (page 989, second paragraph; Fig. 1B and C). Therefore, the amount of initial target nucleic acid can be determined using a reference sample (internal control) for quantitation (page 990; page 991, paragraphs 1-3; Fig. 4).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the real-time detection methods of Leone et al. and Heid et al. to detect ribozymes in transfected plants of Uijteawaal et al. The motivation to do so, as provided by Leone et al., would have been that (page 2155, last paragraph):

“... the novel technology presented in this report offers a truly homogeneous assay in which amplification and detection of RNA occur in one-tube. Compared to current RNA probing and/or blotting methods, the use of molecular beacons to detect NASBA amplicons, retains the same level of specificity and sensitivity, is easy to perform and timesaving, due to a reduction of handling steps. The risk of carry-over contamination is minimized by the advantage of performing the entire method in unopened vessels. Furthermore the assay is sensitive and robust, as demonstrated by working with very complex samples such as potato tuber extracts. This shows that AmpliDet RNA has the potential to be used in routine settings for high-throughput sample analysis.”

The motivation to do so, provided by Heid et al., would have been that, as stated by Heid et al. (page 992, first and second paragraphs):

“Second, this method supports the use of normalization gene (i.e., β -actin) for quantitative PCR or housekeeping genes for quantitative RT-PCR controls. Analysis is performed in real time during the log phase of product accumulation. Analysis during log phase permits many different genes (over a wide input target range) to be analyzed simultaneously, without concern of reaching reaction plateau at different cycles. This will make multigene analysis much easier to develop, because individual internal competitors will not be needed for each gene under analysis. Third, sample throughput will increase dramatically with the new method because there is no post-PCR processing time. ... The real-time PCR method is highly reproducible. Replicate amplifications can be analyzed for each sample minimizing potential error. The system allows for a very large assay dynamic range (approaching 1,000,000-fold starting target). Using a standard curve for the target of interest, relative copy number values can be determined for any unknown sample.”

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11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 6, 2005

TERESA STRZELECKA
PATENT EXAMINER
Teresa Strzelecka

Notice to Comply	Application No.	Applicant(s)	
	09/937,519	KRUPP, GUIDO	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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